Multiple Sclerosis Therapy
A Practical Guide

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Summary

A growing amount of evidence suggests that a disturbance of immunological function is of importance in the pathogenesis of multiple sclerosis. This is reflected in the drugs used to slow progression and to treat relapses. Immunosuppressive drugs such as azathioprine, cyclophosphamide and cyclosporin might have some potential to slow down progression of multiple sclerosis, but their use is limited by potentially serious adverse effects. Recently, it was shown that interferon-β-1b can diminish the exacerbation rate in multiple sclerosis without leading to unacceptable adverse effects. Nevertheless, symptomatic treatment remains of crucial importance in the management of multiple sclerosis patients. Spasticity, depression, fatigue and urinary, paroxysmal and sensory symptoms can all be alleviated to some extent with pharmacological interventions, although rehabilitation procedures and psychosocial consultations are no less important.

Further therapeutic approaches to multiple sclerosis will be directed at either the specificity of the immune response or the grade of activation of the immune response. Magnetic resonance imaging techniques will play an important role in the evaluation of efficacy of new therapeutic agents.
Multiple sclerosis is an inflammatory demyelinating disease of the CNS. In its early stages the disease in general follows a relapsing and remitting course. The majority of patients have recognisable clinical syndromes, because multiple sclerosis lesions have a predilection for certain sites within the CNS: the most common presenting symptoms are paraesthesia in the extremities, optic neuritis and weakness of the limbs.

Although some patients fully recover after each relapse, in many patients recovery tends to be incomplete after some exacerbations and they are left with disability. Many of these patients subsequently enter a progressive phase of the disease during which motor abnormalities (weakness, spasticity), brainstem involvement (internuclear ophthalmoplegia, pseudobulbar palsy) and cerebellar disturbances (ataxia, tremor) can be very disabling. Other symptoms, such as fatigue, loss of bladder and bowel control and neuropsychological abnormalities, are commonly encountered. In about 10 to 20% of patients the disease has a progressive course from onset.

The diagnosis of the disease remains essentially clinical, with demonstration of signs and symptoms disseminated in time and space being required, although a number of investigative procedures have come into use as diagnostic aids to exclude other diseases and help fulfil diagnostic requirements. Cerebrospinal fluid (CSF) examination (elevated IgG index, oligoclonal banding), evoked potential testing (conduction disturbances) and especially magnetic resonance imaging (multiple white matter lesions, indicating dissemination in place) have been shown to increase diagnostic sensitivity.

The pathological hallmark of the disease is the white matter plaque, a clearly defined patch of demyelination within the CNS. In normally myelinated tracts the axons are wrapped in myelin sheaths that are produced by a specialised cell, the oligodendrocyte. Following demyelination, conduction is slowed or lost and symptoms ensue. Histologically, acute lesions are characterised by inflammatory cell infiltration (mainly lymphocytes and macrophages) and demyelination. Chronic lesions show only little inflammatory activity; the myelin sheaths and oligodendrocytes are absent and axonal loss tends to occur.

At present it is not known whether the progressive phase of the disease is mainly due to persistent demyelination, to failure of remyelination, or to occurrence of axonal loss.

1. Magnetic Resonance Imaging

Magnetic resonance imaging shows areas of increased signal intensity on standard images in 95% of patients with clinically definite multiple sclerosis.\[1\] Histopathologically, these abnormalities correspond well with the presence of plaques. The fact that every stage in the development of plaques increases the signal on standard magnetic resonance images explains the poor specificity of these signal changes per se. Following injection of gadolinium salts, signal enhancement can be observed in active lesions, indicating the presence of blood-brain barrier disruption in the inflammatory phase.\[2\]

Monthly magnetic resonance imaging studies have revealed a considerable amount of clinically silent disease activity in patients with relapsing-remitting\[3\] and secondary progressive\[4\] multiple sclerosis. Serial magnetic resonance imaging is 5 to 10 times more sensitive than clinical monitoring in the detection of disease activity. In addition, the nature of the information is more objective than clinical scoring. Magnetic resonance imaging is therefore well suited to serve as an outcome measure in treatment trials. In phase III trials the accumulation of lesions can be used as a secondary endpoint, whereas in early phase II studies magnetic resonance imaging activity can be used as a measure of efficacy.

Guidelines have been developed on how to perform magnetic resonance imaging–monitored treatment trials.\[5\] Based on natural history data, magnetic resonance imaging–monitored treatment trials have been simulated to obtain power estimates. Using a placebo-controlled, parallel group design, moderate treatment effects can be demonstrated in relatively small patient groups within 6...